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First stereoselective synthesis of synargentolide A and revision of absolute stereochemistry

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ABSTRACT

The first stereoselective total synthesis of synargentolide A isolated from *Syncolostemon argenteus* has been achieved from commercially available (*R*)-benzyl glycidyl ether using Sharpless asymmetric epoxidation and cross-metathesis reactions as the key steps. Comparing the spectral data of the synthesized and naturally occurring synargentolide A, the C4′ and C6′- stereogenic centers of the natural synargentolide A were assigned a corrected *anti* relationship.

Naturally isolated 6-substituted-α,β-unsaturated-δ-lactones gained great attention of researcher due to their cytotoxic and *anti*-tumor properties.[1] In addition they inhibit HIV protease,[2] induce apoptosis,[3,4] and have proven to be *anti*-leukemic,[5] along with having many other relevant pharmacological properties.[6] Synargentolide A (**1**),[7] spicegerolide (**2**),[8] hyptolide (**3**),[9] synrotolide (**4**),[10] and anamarine (**5**)[11] isolated from *Syncolostemon* and *Hyptis* species are examples of α,β-unsaturated δ-lactones (Fig. 1). Due to their pharmacological properties, these molecules became the interesting synthetic goals. The structure of synargentolide A was proposed to be **1** by Davies-Coleman and Rivett[7] on the basis of spectroscopic findings, Mosher ester analysis, and acetonide formations. Alberto Marco et al.[12] synthesized the published structure of synargentolide A **1** and found that the spectroscopic data of the synthetic product did not match with those reported for the natural product and therefore stated that the proposed structure for the synargentolide A **1** differs from the actual one.

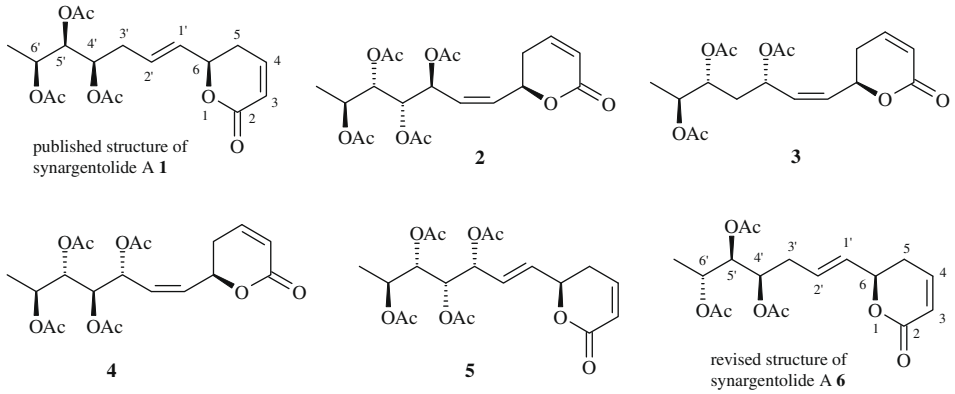

Figure 1. Polyoxygenated lactones.

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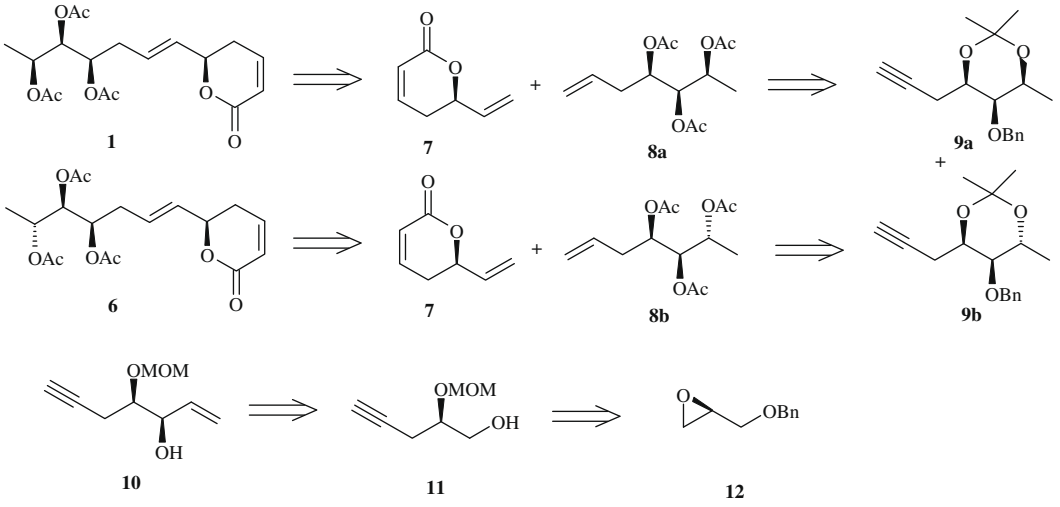
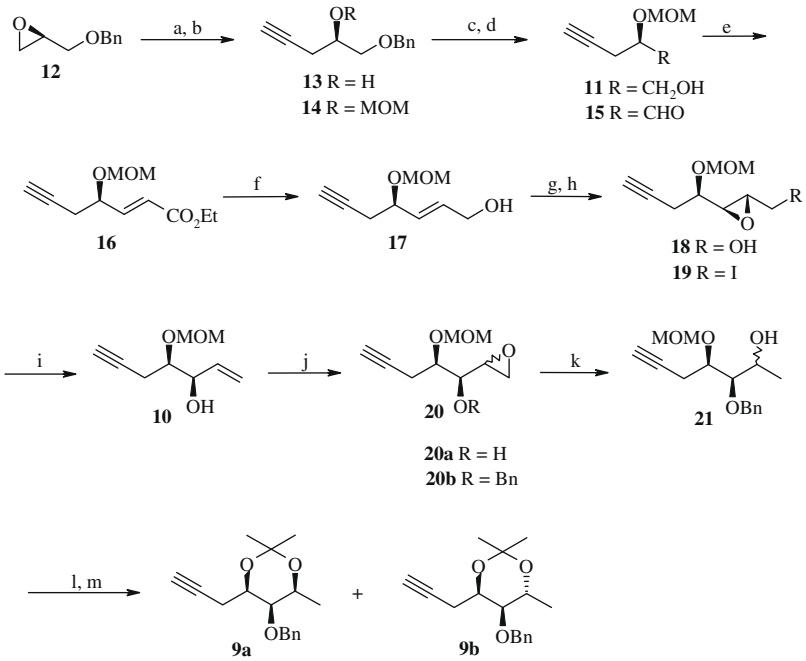
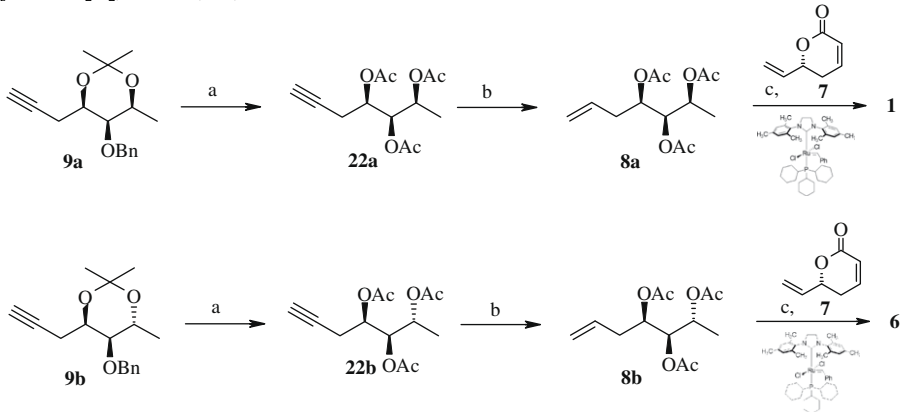


Scheme 1. Retrosynthetic analysis for the published and revised structures of synargentolide A.



Scheme 2. Reagents and conditions: (a) ≡ –Li, DMSO, 0 °C to rt, 1 h, 92%; (b) DIEA, MOM–Cl, 2 h, 0 °C to rt, 95%; (c) Li/liq NH_3, −33 °C, anhydrous THF, 0.5 h, 90%; (d) IBX, DMSO, anhydrous CH_2Cl_2, 0 °C to rt, 24 h, 95%; (e) PPh_3=$CHCO_2Et$, Ph–H, rt, 2 h, 85%; (f) DIBAL-H, anhydrous CH_2Cl_2, −20 °C, 1 h, 75%; (g) L-(+) DIPT, $Ti(O^iPr)_4$, cumenehydroperoxide, anhydrous CH_2Cl_2, −24 °C, 4 h, 98%; (h) TPP, I_2, imidazole, Et_2O/CH_3CN, (3:1) 0 °C to rt, 20 min 92%; (i) Zn dust, EtOH, reflux, 2 h, 92%; (j) (a) *m*-CPBA, $NaHCO_3$, anhydrous CH_2Cl_2, −10 °C, 10 h, 92%, dr (1:1); (b) BnBr, NaH, anhydrous THF, 0 °C to rt, 3 h, 95%; (k) $LiAlH_4$, anhydrous THF, 0 °C to rt, 0.5 h, 95%; (l) 2 N HCl, rt, 5 h, 93%; (m) 2,2-DMP, PPTS, anhydrous CH_2Cl_2, 0 °C to rt, 1 h, 95%.



Scheme 3. Reagents and conditions: (a) (i) Li/liq NH_3, anhydrous THF, −33 °C, 0.5 h, 91%; (ii) MeOH, 2 N HCl, rt, 1 h, 93%; (iii) Ac_2O, TEA, DMAP, anhydrous CH_2Cl_2, 0 °C to rt, 0.5 h, 94%; (b) $Pd/CaCO_3$, quinoline, HPLC–EtOAc, rt, 2 h, 92%; (c) Gr-II, refluxing anhydrous CH_2Cl_2, 2 h, 65%.

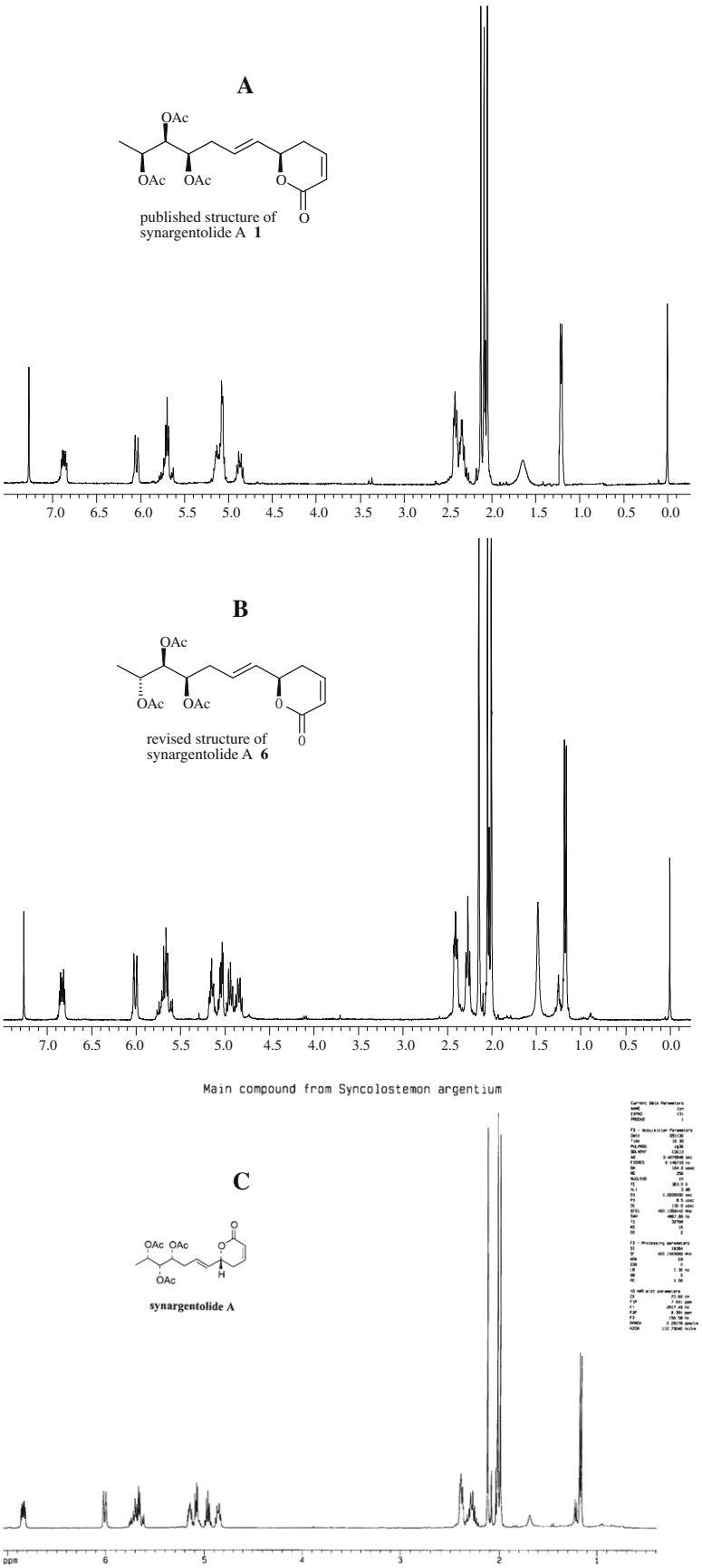


Figure 2. Comparison of the ^{1}H NMR spectra of the synthetic lactones **1** (A) and **6** (B) with that of natural synargentolide A (C).

As a part of our current interest in naturally occurring, pharmacologically active δ-lactones,[13] we became interested in the synthesis of synargentolide A and to determine the absolute configuration of the natural product.

The retrosynthesis is outlined in Scheme 1. The target molecule **1** (published structure)[7] and **6** (revised structure) could be prepared independently by cross-metathesis reaction of **8a** and **8b** with vinyl lactone **7**. The substrates **8a** and **8b** in turn could be obtained from the commercially available (*R*)-benzyl glycidyl ether **12** by sequential reactions.

The synthesis began with the commercially available (*R*)-benzyl glycidyl ether **12** (Scheme 2). Accordingly the ring opening of epoxide **12** with lithium acetylide ethylene diamine complex provided chiral homopropargyl alcohol **13** in 92% yield. The secondary hydroxyl group in compound **13** was protected as its MOM ether **14** using MOMCl and Hunig's base and the subsequent removal of benzyl group furnished alcohol **11**. Oxidation of **11** using IBX in DMSO/DCM gave the corresponding aldehyde **15**, which was subjected to a Wittig reaction with the stable ylide to afford α,β-unsaturated ester **16**. After reduction of **16** to allylic alcohol **17** (75%) using DIBAL-H, Sharpless asymmetric epoxidation delivered epoxy alcohol **18** in 98% yield as a single diastereomer, which was elaborated to allylic alcohol **10** by an iodination/reductive ring-opening sequence.

Epoxidation of the terminal double bond in **10** using *m*-CPBA provided an inseparable mixture of epoxy alcohol **20a** in a ratio of 1:1 (92% combined yield). After protection of the secondary hydroxyl group as benzyl ether, the resulting compound **20b** was treated with LAH to give an alcohol again as an inseparable mixture (**21**). The MOM group was deprotected and a 1,3-diol function in compound **21** was protected as acetonide by 2,2-dimethoxypropane in the presence of PPTS and the resulting acetonides **9a** and **9b** were easily separable by flash chromatography. In order to confirm the relative configuration of 1,3-acetonides **9a** and **9b**, ^{13}C NMR chemical shifts were studied. The two methyl groups in the acetonide part in **9a** resonated at 19.0 and 29.6 ppm indicating that the two hydroxyl groups are in a 1,3-*syn* orientation and further substantiated by the appearance of the quaternary carbon in the down-field region (98.8 ppm).[14] In contrast, for the acetonide derivative **9b** signals were found at 24.8 and 23.8 ppm and quaternary carbon at 100.7 ppm, which were characteristic for the methyl groups in the acetonide part of 1,3-*anti* diol.[14]

To determine the correct absolute configuration of natural synargentolide A, both isomers of synargentolide A **1** and **6** were synthesized by the following steps from **9a** and **9b** as shown in Scheme 3.

Removal of benzyl and acetonide groups, followed by acetylation of the three hydroxy groups was performed to provide **22a** in 95% yield (Scheme 3). The terminal triple bond was reduced partially to double bond under Lindlar's conditions to afford **8a**. Finally, the cross-metathesis reaction between **8a** and vinyl lactone **7**[13j] was smoothly performed using Grubbs' second generation catalyst to give the published structure of synargentolide A **1** (Fig. 2). This did not turn out to be identical with the natural product but matched with the synthesized product.[12]

In a similar fashion, synthesis of **6** was commenced from **9b** (Scheme 3) independently repeating the steps as in the case of **1** and the target molecule **6** was obtained in good yield. The spectral properties (Fig. 2) and optical rotation of the synthetic compound **6** were found to be identical with those published for the natural synargentolide A **1** {$[\alpha]_D^{25}$ +36.5 (*c* 1, $CHCl_3$), lit.[7] $[\alpha]_D^{25}$ +40 (*c* 1.1, $CHCl_3$)}. Therefore, the structure of natural product stands revised to be of **6**.

In conclusion, we have performed a stereoselective synthesis of the natural synargentolide A and shown it to be **6**.[15] Synargentolide A is therefore 6*R*[4*R*,5*R*,6*R*-triacetyloxy-1*E*-heptenyl]-5,6-dihydro-2*H*-pyran-2-one. Sharpless asymmetric epoxidation (SAE) and cross-metathesis (CM) are the key reactions involved.

Acknowledgments

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15. Analytical data of all the new compounds are given below:
Compound **1**: $[\alpha]_D^{25}$ +12.5 (*c* 1, $CHCl_3$); IR (KBr) 1738, 1374, 1221, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 (ddd, *J* = 8.8, 4.0, 2.4 Hz, 1H), 6.02 (dt, *J* = 10.4, 2.4 Hz, 1H), 5.75–5.63 (m, 2H), 5.15 (m, 1H), 5.08 (dt, *J* = 7.2, 4.0 Hz, 1H, CH), 4.96 (m, 1H, CH), 4.86 (m, 1H, CH), 2.39 (m, 2H, CH_2), 2.28 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.0 (s, 3H, CH_3), 1.18 (d, *J* = 6,4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 170.1, 170.0, 163.8, 144.5, 130.9, 128.3, 121.5,

77.2, 73.7, 69.6, 69.3, 34.0, 29.5, 21.0, 20.8, 20.7, 16.0; HRMS calcd for $C_{18}H_{24}O_8Na$: 391.1368; found: 391.1355.

Compound **8a**: $[\alpha]_D^{25}$ +1.5 (*c* 1, $CHCl_3$); IR (KBr) 1742, 1370, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.66 (m, 1H), 5.30–4.93 (m, 5H), 2.35–2.14 (m, 2H), 2.06 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.15 (d, *J* = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 170.0, 169.9, 132.0, 118.8, 74.2, 70.2, 68.7, 35.3, 121.0, 20.8, 20.6, 16.3.

Compound **8b**: $[\alpha]_D^{25}$ +22.5 (*c* 1, $CHCl_3$); IR (KBr) 1744, 1372, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.69 (m, 1H), 5.16 (dt, *J* = 7.0, 3.1 Hz, 1H, CH), 5.11–5.03 (m, 3H), 4.94 (m, 1H, CH), 2.24 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.0 (s, 3H, CH_3), 1.18 (d, *J* = 6.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9. 169.8, 169.7, 132.2, 118.4, 73.7, 69.7, 67.2, 35.4, 20.8, 20.6, 20.5, 15.9; HRMS calcd for $C_{13}H_{20}O_6Na$: 295.1157; found: 295.1149.

Compound **9a**: $[\alpha]_D^{25}$ −42.0 (*c* 1, $CHCl_3$); IR (KBr) 2985, 1455, 1378, 1229, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.21 (m, 5H, ArH), 4.72 (ABq, *J* = 11.3 Hz, 2H, C*H*$_2$-OAr), 3.97 (m, 2H), 3.29 (m, 1H, CH), 2.68 (dd, *J* = 2.6, 16.4 Hz, 0.5H), 2.65 (dd, *J* = 2.4, 10.0 Hz, 0.5H), 1.98 (m, acetylinic CH), 1.43 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.18 (d, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 128.2, 128.1, 127.6, 98.8, 80.6, 75.0, 72.8, 71.6, 70.6, 68.5, 29.6, 29.3, 19.0, 17.7; HRMS calcd for $C_{17}H_{22}O_3Na$: 297.1466; found: 297.1465.

Compound **9b**: $[\alpha]_D^{25}$ −19.5 (*c* 1, $CHCl_3$); IR (KBr) 2990, 1455, 1377, 1202, 1083 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.23 (m, 5H, ArH), 4.61 (ABq, *J* = 11.7 Hz, 2H, C**H$_2$**-OAr), 4.0, (m, 1H, CH), 3.74 (m, 1H, CH), 3.40 (m, 1H, CH), 2.62 (dd, *J* = 2.9, 16.5 Hz, 0.5H), 2.60 (dd, *J* = 2.9, 16.5 Hz, 0.5H), 2.42 (dd, *J* = 2.9, 16.5 Hz, 0.5H), 2.41 (dd, *J* = 2.9, 16.5 Hz, 0.5H), 1.92 (m, acetylinic CH), 1.35 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.19 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 128.3, 127.9, 127.7, 100.7, 82.1, 81.0, 74.1, 69.7 (×2C), 69.1, 24.8, 23.8, 20.0, 19.4; HRMS calcd for $C_{17}H_{22}O_3Na$: 297.1466; found: 297.1457.

Compound **10**: $[\alpha]_D^{25}$ −10.0 (*c* 1, $CHCl_3$); IR (KBr) 3446, 3295, 2897, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.85 (m, 1H), 5.40 (m, 1H), 5.23 (m, 1H), 4.76 (d, *J* = 6.5 Hz, 1H), 4.70 (d, *J* = 7.3 Hz, 1H), 4.22 (m, 1H, CH), 3.57 (m, 1H, CH), 3.41(s, 3H, CH_3), 2.62–2.35 (m, 2H, CH_2), 1.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7, 117.2, 96.7, 80.3, 79.3, 73.4, 70.2, 55.8, 21.2; HRMS calcd for $C_9H_{14}O_3Na$: 193.0840; found: 193.0848.

Compound **11**: $[\alpha]_D^{25}$ −71.6 (*c* 1, $CHCl_3$); IR (KBr) 3437, 3293, 2932, 1640, 1363, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.72 (m, 2H, CH_2), 3.77–3.68 (m, 2H, CH_2), 3.59 (m, 1H, CH), 3.41 (s, 3H, CH_3), 2.43 (m, 2H, CH_2), 1.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.5, 78.1, 70.2, 64.3, 55.6, 36.2, 21.6; HRMS calcd for $C_7H_{12}O_3Na$: 167.0684; found: 167.0684.

Compound **6**: $[\alpha]_D^{25}$ +36.5 (*c* 1, $CHCl_3$); IR (KBr) 1738, 1374, 1221, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 (ddd, *J* = 8.8, 4.0, 2.4 Hz, 1H), 6.02 (dt, *J* = 10.4, 2.4 Hz, 1H), 5.75–5.63 (m, 2H), 5.15 (m, 1H), 5.08 (dt, *J* = 7.2, 4.0 Hz, 1H, CH), 4.96 (m, 1H, CH), 4.86 (m, 1H, CH), 2.39 (m, 2H, CH_2), 2.28 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.0 (s, 3H, CH_3), 1.18 (d, *J* = 6,4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl3): δ 170.2, 170.1, 170.0, 163.8, 144.5, 130.9, 128.3, 121.5, 77.2, 73.7, 69.6, 69.3, 34.0, 29.5, 21.0, 20.8, 20.7, 16.0; HRMS calcd for $C_{18}H_{24}O_8Na$: 391.1368; found: 391.1355.